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Zeichen/Ref./Réf.	Anmeldung Nr./Application No./Demande n°./Patent Nr./Patent No./Brevet n°.
GWS 19943	96903690.4

Anmelder/Applicant/Demandeur/Patentinhaber/Proprietor/Titulaire
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COMMUNICATION

The European Patent Office herewith transmits

- ☐ the European search report
- ☐ the declaration under Rule 45 EPC
- ☐ the partial European search report under Rule 45 EPC
- ☒ the supplementary European search report concerning the international application under Article 157(2) EPC relating to the above-mentioned European patent application. Copies of the documents cited in the search report are enclosed.

The following specifications given by the applicant have been approved by the Search Division :

☐ Abstract ☐ Title ☐ Figure

☐ The abstract was modified by the Search Division and the definitive text is attached to this communication.

☐ The following figure will be published with the abstract, since the Search Division considers that it better characterises the invention than the one indicated by the applicant.

Figure:

☐ Additional copy(copies) of the documents cited in the European search report.

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REFUND OF THE SEARCH FEE

If applicable under Article 10 Rules relating to fees, a separate communication from the Receiving Section on the refund of the search fee will be sent later.

European Patent Office

SUPPLEMENTARY EUROPEAN SEARCH REPORT

Application Number
EP 96 90 3690

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
X	CHEMICAL ABSTRACTS, vol. 106, no. 19, 11 May 1987 Columbus, Ohio, US; abstract no. 156843v, UBUKA, TOSHIHIKO ET AL: "Synthesis of disulfides related to glutathione and their detection in tissue" XP002052798 * page 728, column 2 * & GANRYU AMINOSAN, vol. 8, no. 1, 1985, JAPAN, pages 153-157, ---	1,4	A61K31/44 A61K38/05 A61K38/06 A61K38/07 A61K38/08 C07C321/14 C07C321/28 C07D213/70 C07H19/048 C07H21/00 C07K16/38 C08G69/04 C12N9/08
X	EP 0 482 766 A (KYOWA HAKKO KOGYO KK) 29 April 1992 * page 2 - page 3 * ---	1-4	
X	WO 91 16067 A (RES CORP TECHNOLOGIES INC) 31 October 1991 * claim 12 * ---	1-4	
X	STN INFORMATION SERVICE: FILE REG, XP002052828 * See RN 23130-02-1 * ---	1-5	TECHNICAL FIELDS SEARCHED (Int.Cl.6) C07D A61K C07H C12N C07C
X	PATENT ABSTRACTS OF JAPAN vol. 013, no. 056 (C-566), 8 February 1989 & JP 63 246382 A (KARUPISU SHOKUHIN KOGYO KK), 13 October 1988, * abstract * -----	12,14	

The supplementary search report has been drawn up for the claims attached hereto.

Place of search	Date of completion of the search	Examiner
MUNICH	21 January 1998	Arias-Sanz, J

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

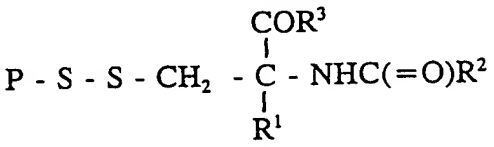
T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C04)

WHAT IS CLAIMED IS:

1. A compound of general formula VI



VI

in which P is selected from the group consisting of peptides, proteins and oligonucleotides; R^1 is hydrogen, lower alkyl or aryl; R^2 is a lipid-containing moiety comprising a lipid group; and R^3 is -OH, a lipid-containing moiety comprising a lipid group or an amino acid chain comprising one or 2 amino acids and terminating in $-CO_2H$ or $-COR^2$.

2. A compound according to claim 1, wherein R^1 is hydrogen, R^2 is a lipid group and R^3 is -OH.

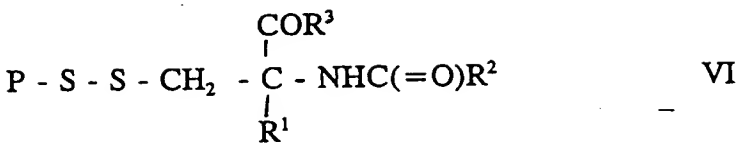
3. A compound according to claim 1, wherein R^1 is hydrogen, R^2 is $-CH_2CH_2CH(NH_2)CO_2H$ or $-CH_2CH_2CH(NHCO\text{-lipid})CO\text{-lipid}$ and R^3 is $-NHCH_2CO_2H$ or $-NHCH_2CO$-lipid in which at least one of R^2 and R^3 comprises a lipid group.

4. A compound according to claim 1, wherein said lipid group is a hydrophobic substituent comprising about 4 to about 26 carbon atoms.

5. A compound according to claim 4, wherein said lipid group is a hydrophobic substituent comprising about 5 to about 19 carbon atoms.

6. A method for increasing absorption of a sulfhydryl-group containing compound selected from the group consisting of peptides, proteins and oligonucleotides into mammalian cells, said method comprising:

forming from the sulfhydryl-containing compound a compound of general formula VI



VI

in which P is a moiety derived from the sulfhydryl-group containing compound selected from the group consisting of peptides, proteins and oligonucleotides; R^1 is hydrogen, lower alkyl or aryl; R^2 is a lipid-containing moiety; and R^3 is -OH, a lipid-containing moiety or an amino acid chain comprising one or 2 amino acids and terminating in $-CO_2H$ or $-COR^2$; and

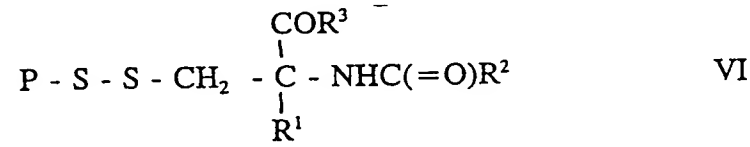
administering the compound of general formula VI to the cells.

7. A method according to claim 6, wherein R^1 is hydrogen, R^2 is a lipid group and R^3 is -OH.

8. A method according to claim 6, wherein R^1 is hydrogen, R^2 is $-CH_2CH_2CH(NH_2)CO_2H$ or $-CH_2CH_2CH(NHCO\text{-lipid})CO\text{-lipid}$ and R^3 is $-NHCH_2CO_2H$ or $-NHCH_2CO$-lipid in which at least one of R^2 and R^3 comprises a lipid group.

9. A method for prolonging blood and tissue retention of a sulfhydryl-group containing compound selected from the group consisting of peptides, proteins and oligonucleotides into mammalian cells, said method comprising:

forming from the sulfhydryl-containing compound a compound of general formula VI



VI

in which P is selected from the group consisting of peptides, proteins and oligonucleotides; R^1 is hydrogen, lower alkyl or aryl; R^2 is a lipid-containing moiety; and R^3 is -OH, a lipid-containing moiety or an amino acid chain comprising one or 2 amino acids and terminating in $-CO_2H$ or $-COR^2$; and

administering the compound of general formula VI to the cells.

10. A method according to claim 9, wherein R^1 is hydrogen, R^2 is a lipid group and R^3 is -OH.

11. A method according to claim 9, wherein R^1 is hydrogen, R^2 is $-CH_2CH_2CH(NH_2)CO_2H$ or $-CH_2CH_2CH(NHCO\text{-lipid})CO\text{-lipid}$ and R^3 is $-NHCH_2CO_2H$ or $-NHCH_2CO$-lipid in which at least one of R^2 and R^3 comprises a lipid group.

12. A compound of general formula V

$$A - S - S - CH_2 - CR^1(NHCOR^2)C(=O)R^3 \qquad V$$

in which A is an aromatic activating residue; R^1 is hydrogen, lower alkyl or aryl; R^2 is a lipid-containing moiety comprising a lipid group; and R^3 is -OH, a lipid-containing moiety comprising a lipid group or an amino acid chain comprising one or 2 amino acids and terminating in $-CO_2H$ or $-COR^2$.

13. A compound according to claim 12, wherein A is 2-pyridyl or 4-nitrophenyl.

14. A compound according to claim 12, wherein R^1 is hydrogen, R^2 is a lipid group and R^3 is -OH.

15. A compound according to claim 12, wherein R^1 is hydrogen, R^2 is $-CH_2CH_2CH(NH_2)CO_2H$ or $-CH_2CH_2CH(NHCO\text{-lipid})CO\text{-lipid}$ and R^3 is $-NHCH_2CO_2H$ or $-NHCH_2CO$-lipid in which at least one of R^2 and R^3 comprises a lipid group.

16. A method for a forming a compound of general formula VI, comprising:

reacting a compound of general formula PSH, in which P is selected from the group consisting of peptides, proteins and oligonucleotides, with a compound of general formula V

$$A - S - S - CH_2 - CR^1(NHCOR^2)C(=O)R^3 \qquad V$$

in which A is an aromatic activating residue; R^1 is hydrogen, lower alkyl or aryl; R^2 is a lipid-containing moiety comprising a lipid group; and R^3 is -OH,

a lipid-containing moiety comprising a lipid group or an amino acid chain comprising one or 2 amino acids and terminating in $-CO_2H$ or $-COR^2$.

17. A method according to claim 16, wherein A is 2-pyridyl or 4-nitrophenyl.

18. A method according to claim 16, wherein R^1 is hydrogen, R^2 is a lipid group and R^3 is -OH.

19. A method according to claim 16, wherein R^1 is hydrogen, R^2 is $-CH_2CH_2CH(NH_2)CO_2H$ or $-CH_2CH_2CH(NHCO\text{-lipid})CO\text{-lipid}$ and R^3 is $-NHCH_2CO_2H$ or
$-NHCH_2CO$-lipid in which at least one of R^2 and R^3 comprises a lipid group.

20. A compound of general formula III

$$A - S - S - CH_2 - CR^1(NH_2)C(=O)R^{3'} \qquad III$$

in which $R^{3'}$ is -OH or an amino acid chain comprising one or two amino acids and terminating in $-CO_2H$; A is an aromatic activating residue; and R^1 is hydrogen, lower alkyl or aryl.

21. A compound according to claim 20, wherein R^1 is hydrogen and $R^{3'}$ is -OH.

22. A compound according to claim 20, wherein R^1 is hydrogen and R^3 is $-NHCH_2CO_2H$.

23. Use of a compound of formula VI as set out in any of Claims 1–5 in manufacture of a medicament for prolonging blood and tissue retention of a sulfhydryl–group containing compound selected from the group consisting of peptides, proteins and oligonucleotides.

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 96 90 3690

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
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21-01-1998

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